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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,936	08/16/99	OPPERMANN	H STK-077

EXAMINER	
ROMEO, D	
ART UNIT	**PAPER NUMBER**
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TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON MA 02110

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/374,936	Oppermann et al.
Examiner	**Art Unit**
David Romeo	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1 May 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) *4 and 7-17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 5, and 6* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-17* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: *Errors corrected by STIC*

DETAILED ACTION

1. Applicant's election of Group I, claims 1-7, and the species a, c, e, and f in Paper No. 9 is acknowledged. Applicant's election of the finger 1 domain of hOP-1 (amino acid residues 2-29 of SEQ ID NO: 55), the finger 2 domain of CDMP-2 (amino acid residues 68-98 of SEQ ID NO: 86), the heel domain of hOP-1 (amino acid residues 35-65 of SEQ ID NO: 55), and the C-terminal Cys domain of hOP-1 (SEQ ID NO: 55) in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 4, 7-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9 and 11.

3. Claims 1-3, 5, 6 are being examined to the extent that they read upon the elected invention.

4. Upon further consideration the restriction requirement is recast below. Applicants election of a, c, e, and f and the finger 1 domain of hOP-1 (amino acid residues 2-29 of SEQ ID NO: 55), the finger 2 domain of CDMP-2 (amino acid residues 68-98 of SEQ ID NO: 86), the

heel domain of hOP-1 (amino acid residues 35-65 of SEQ ID NO: 55), and the C-terminal Cys domain of hOP-1 (SEQ ID NO: 55) has constructively elected the finger 1 domain of hOP-1, the heel domain of hOP-1, the finger 2 domain of CDMP-2, the conserved C-terminal cysteine domain of hOP-1, and the species amino acid residues 2-29 of SEQ ID NO: 55, amino acid residues 68-98 of SEQ ID NO: 86, amino acid residues 35-65 of SEQ ID NO: 55, and the C-terminal Cys domain of hOP-1 (SEQ ID NO: 55) for prosecution on the merits.

Election/Restriction

5. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, drawn to a protein comprising a dimer wherein the monomers are chimeras of TGF-β superfamily members, classified in class 530, subclass 350.

II. Claims 8-14, to the extent that they are drawn to a recombinant method of protein synthesis, classified in class 435, subclass 69.7.

III. Claims 9-14, to the extent that they are drawn to an enzymatic method of protein synthesis, classified in class 435, subclass 68.1.

IV. Claims 9-14, to the extent that they are drawn to a non-recombinant method of protein synthesis, classified in class 530, subclass 333.

V. Claims 15-16, drawn to a method of tissue regeneration, classified in class 514, subclass 12.

VI. Claim 17, drawn to an immunoassay, classified in class 435, subclass 7.1.

6. The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case I could be made with III or IV.

Inventions III and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case I could be made with II or IV.

Inventions IV and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case I could be made with II or III.

Inventions I and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the

product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case I could be used in vitro for the structure-function analysis of a TGF-β superfamily member or could be used in VI.

Inventions I and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case I could be used in vitro for the structure-function analysis of a TGF-β superfamily member or could be used in V.

The following pairwise combinations of methods are independent and distinct, wherein each member of a pair performs different functions, using different starting materials and/or process steps: II and each of III-VI; III and each of IV-VI; IV and each of V-VI; V and VI.

7. Groups I-VI are generic to a plurality of disclosed patentably distinct inventions comprising a single invention represented by:

a single invention selected from the group consisting of

a. a finger 1 subdomain derived from a second, different, single member of the TGF-β superfamily; and

b. a finger 1 subdomain derived from a third, different, single member of the

TGF-β superfamily; and,

a single invention selected from the group consisting of

c. a heel subdomain derived from a second, different, single member of the TGF-β superfamily; and,

d. a heel subdomain derived from a third, different, single member of the TGF-β superfamily.

in combination with,

e. a finger 2 subdomain derived from a first single member of the TGF-β superfamily;

f. a conserved C-terminal cysteine domain of a single member of the TGF-β superfamily.

Applicants can elect a group to be examined by specifying a single invention of either a or b, a single invention of either c or d, and the inventions e and f. For example, a proper election would be a, c, e, and f. Applicant has already constructively elected an invention for prosecution on the merits.

Each of the inventions is independent and distinct, wherein each can be manufactured independently of the other and used for independent and distinct purposes.

Figure 1 sets forth 37 TGF-β superfamily members. For each finger 1 domain, finger 2

domain, heel domain, and conserved C-terminal domain there are 37 independent and distinct inventions. It follows that there are 37x37x37x37=1874161 independent and distinct inventions. It is beyond the resources of the PTO to individually set forth each invention.

8. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

9. Because these inventions are distinct for the reasons given above and the searches required are not coextensive, restriction for examination purposes as indicated is proper.

10. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

11. Claim 10 is generic to a plurality of disclosed patentably distinct species comprising the species listed in claim 10.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed, and consonant with the election of species in the preceding species elections. Applicant has already constructively elected an invention for prosecution on the merits.

Each of the species is independent and distinct, wherein each can be manufactured independently of the other and used for independent and distinct purposes.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

12. Claims 15, 16 are generic to a plurality of disclosed patentably distinct species comprising the species listed in claim 16.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed, and consonant with the election of species in the preceding species elections. Applicant has already constructively elected an invention for prosecution on the merits.

Each of the species is independent and distinct, wherein each performs different functions, using different starting materials and/or process steps, and/or with different outcomes.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

13. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37

CFR 1.143).

Applicants election of a, c, e, and f and the finger 1 domain of hOP-1 (amino acid residues 2-29 of SEQ ID NO: 55), the finger 2 domain of CDMP-2 (amino acid residues 68-98 of SEQ ID NO: 86), the heel domain of hOP-1 (amino acid residues 35-65 of SEQ ID NO: 55), and the C-terminal Cys domain of hOP-1 (SEQ ID NO: 55) has constructively elected the finger 1 domain of hOP-1, the heel domain of hOP-1, the finger 2 domain of CDMP-2, the conserved C-terminal cysteine domain of hOP-1, and the species amino acid residues 2-29 of SEQ ID NO: 55, amino acid residues 68-98 of SEQ ID NO: 86, amino acid residues 35-65 of SEQ ID NO: 55, and the C-terminal Cys domain of hOP-1 (SEQ ID NO: 55) for prosecution on the merits.

14. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Formal Matters

15. The disclosure is objected to because of the following informalities: there are blank spaces where U.S. patent application serial NOs. are supposed to be.

Appropriate correction is required.

16. The computer readable form of the sequence listing has been entered after correction of minor errors in the CRF by the Scientific and Technical Information Center staff. Specifically, non-ASCII "garbage" at the end of the file was deleted. Any questions or comments regarding this matter should be directed to the Scientific and Technical Information Center staff member Mark Spencer at 703 308-4212.

17. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. Sequences are disclosed in the figures without the appropriate sequence identifier, i.e. SEQ ID NO:. Applicant may bring the application into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. This is not meant to be an exhaustive list of instances where the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the

"Sequence Listing."

Correction is required.

Claim Rejections - 35 USC § 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite over the recitation of finger 1, finger 2, or heel subdomain because it is unclear if finger 1, finger 2, or heel is intended or if a subdomain of finger 1, finger 2, or heel, as in a portion thereof, is intended. The metes and bounds of the claim(s) are not clearly set forth.

Claims 1, 5 are indefinite over the recitation of "derived from". The term "derived from" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of derivation, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 1-3, 5, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keck (a12) in view of Griffith (v12), Luyten (n12), Qian (u12), Daopin (w12).

Keck teaches a finger 1 domain of OP-1 comprising amino acid residues 2-29 of SEQ ID NO: 55 (column 14, line 43), a heel domain of OP-1 comprising amino acid residues 35-65 of SEQ ID NO: 55 (column 15, line 10), and a conserved C-terminal 7-cys domain of OP-1 that is the conserved C-terminal 7-cys domain of SEQ ID NO: 55 (SEQ ID NO: 16). Sequences for the finger and heel regions may be copied from the respective finger and heel region sequences of any known TGF-β superfamily member identified therein (column 4, lines 58-61). Keck does not teach a chimeric protein comprising a dimer wherein one monomer comprises an OP-1 finger 1 domain (amino acid residues 2 to 29 of SEQ ID NO: 55), a CDMP-2 finger 2 domain (amino acid residues 68-98 of SEQ ID NO: 86), and an OP-1 heel domain (amino acid residues 35 t o 65 of SEQ ID NO: 55, wherein said monomer further comprises an OP-1 conserved C-terminal cysteine skeleton (SEQ ID NO: 55).

Griffith teaches that all of the TGF-β superfamily members in Figure 6 share the OP-1/TGF-β2 structural motif (page 882, right column, full paragraph 1). The finger 2 domain of OP-1 comprises amino acid residues 105 to 139 (Figure 3). Amino acid residues 105 to 139 of OP-1 comprise the first amino acid residue after the third from the last Cys to the C-terminus of the molecule (Figures 1 and 3).

Luyten teaches the amino acid sequence of CDMP-2 (Figure 2). The first amino acid residue after the third from the last Cys to the C-terminus of the molecule comprise amino acid residues 68 to 98 of SEQ ID NO: 86. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that the first amino acid residue after the third from the last Cys to the C-terminus of CDMP-2 comprises a finger 2 domain. CDMP-2 has chondrogenic activity in vivo but substantially no osteogenic activity (page 3, full paragraph 1).

Qian teaches that the use of chimeric molecules is a practical approach to investigating the structure/function relationships in closely related proteins (page 6294, left column, full paragraphs 3-4).

Daopin teaches a close structural similarity between TGF-β2 and BMP-2 (page 372, paragraph bridging columns 2-3, last sentence; Table 2), and suggests that the only stable form of TGF-β2 in solution is a dimer (page 370, column 3, full paragraph 2, last sentence). The interface between the dimers is made largely of hydrophobic residues (page 371, column 1, full paragraph 1).

Griffith, Luyten, Qian, and Daopin do not teach a chimeric protein comprising a dimer wherein one monomer comprises an OP-1 finger 1 domain (amino acid residues 2 to 29 of SEQ ID NO: 55), a CDMP-2 finger 2 domain (amino acid residues 68-98 of SEQ ID NO: 86), and an OP-1 heel domain (amino acid residues 35 t o 65 of SEQ ID NO: 55, wherein said monomer further comprises an OP-1 conserved C-terminal cysteine skeleton (SEQ ID NO: 55). However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a morphon, as taught by Keck, and to modify that teaching by making a chimeric protein comprising a dimer wherein one monomer comprises an OP-1 finger 1 domain (amino acid residues 2 to 29 of SEQ ID NO: 55), a CDMP-2 finger 2 domain (amino acid residues 68-98 of SEQ ID NO: 86), and an OP-1 heel domain (amino acid residues 35 t o 65 of SEQ ID NO: 55, wherein said monomer further comprises an OP-1 conserved C-terminal cysteine skeleton (SEQ ID NO: 55) with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because sequences for the finger and heel regions may be copied from the respective finger and heel region sequences of any known TGF-β superfamily, the use of chimeric molecules would be a practical approach to investigating the structure/function relationships of OP-1 and CDMP-2, and the only stable form in solution of such a chimeric molecule would reasonably be expected to be a dimer.

Conclusion

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Andersson (x12) teaches that mutation of the Cys residues forming interchain disulfide bonds in PDGF to serine residues, gave a molecule with agonistic properties presumably because the molecule still occurred as a dimer (page 163, left column). Murray-Rust (y12) teaches topological similarities in TGF-β2, PDGF-BB, and NGF (Abstract). The extensive mainly hydrophobic interactions seen in dimers of these proteins make it clear that dimerization has been essential for their stability (page 158, left column).

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

JULY 15, 2001